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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/055,711	REBAR ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,22-28 and 30-55* is/are pending in the application.

4a) Of the above claim(s) *1,3,5,23,24,33-35,38 and 42-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,22,25-28,30-32,36-37,39-41 and 53-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/27/2006 has been entered.

Receipt is acknowledged of an amendment, filed 3/27/2006, in which claims 6-21 and 29 were canceled, claims 26 and 30 were amended, and claims 54-55 were newly added. Currently, claims 1-5, 22-28, 30-55 are pending.

Any rejection of record in the previous office actions not addressed herein is withdrawn.

Election/Restrictions

Applicant elected Group II (drawn to nucleic acid), species: DNA target sequence, zinc finger component comprising X(3)-Cys-X(2)-Cys-X(12)-His-X(3)-Z-X(4), target located in a plant cell, and a maize C1 activation domain in the reply filed on 8/3/2004 and 11/18/2004.

The requirement for the election of a specific zinc finger component, as set forth on pages 3-4 of the Office action mailed 7/1/2004 has been withdrawn. The pending claims are no longer recite formulae for distinct zinc finger components. The remainder of the species election requirements is maintained.

Claims 1, 33 and 42-52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking

claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 8/3/2004 and 11/18/2004.

Claims 3, 5, 23-24, 34-35 and 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 8/3/2004 and 11/18/2004.

Currently, claims 2, 4, 22, 25-28, 30-32, 36-37, 39-41 and 53-55 are under consideration.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 32 and 41 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The term "host cell" encompasses a cell residing in a human being. The specification at page 33 states that the host cell comprising the nucleic acid is intended to be re-infused back into the subject, which encompasses a human, for gene therapy purposes. As such, the recitation of the limitation "isolated" would be remedial. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 22, 25-28, 30-32, 36-37, 39-41 and 53-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was made in the Office action mailed 11/15/2005 and has been rewritten to address the amendment to the claims in the reply filed 3/27/2006.

The claims are drawn to an isolated polynucleotide encoding a non-naturally-occurring zinc-finger binding protein comprising a non-canonical zinc finger component, wherein said non-canonical zinc finger component contains a beta turn comprising the two amino-terminal cysteine or histidine zinc coordinating residues and an alpha helix comprising the two carboxy-terminal cysteine or histidine zinc coordinating residues, and at least one of the amino-terminal zinc coordinating residues is a histidine residue or at least one of the carboxy-terminal zinc coordinating residues is a cysteine residue and wherein the protein is engineered to bind to a target sequence. Thus, the claims are drawn to a genus of compounds that is defined by secondary structure (beta turn and alpha helix), primary structure (cysteine and histidine zinc coordinating residues that differ from the canonical C2H2 consensus), and function in that they must be capable of binding to a target sequence. Given the structural limitations of the claims, the primary structure must be capable of providing the information necessary to allow the protein to fold into the recited secondary structures.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus.

The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In the instant case, while the claims contain a description of a general structure drawn to the non-canonical zinc finger component containing a beta turn comprising the two amino-terminal cysteine and histidine zinc coordinating residues and an alpha helix comprising the two carboxy-terminal cysteine and histidine zinc coordinating residues, the structure is further limited by excluding the C2H2 structure which supports that structure, instead claiming a retention of the structure without use of the standard C2H2 zinc coordinating residues. In other words, what is claimed is a structure where the critical C2H2 residues, which are used to support the structure, have been replaced with amino acid residues that are not C2H2 (and whatever other amino acid changes are needed to support that replacement of the zinc coordinating residue(s)). While cysteine and histidine are both known to coordinate zinc atoms in the context of properly folded zinc fingers, these critical amino acids are not predictably interchanged (Green et al. Biochem J., Vol. 333, pages 85-90, 1998). For example, Green et al teach that the conversion of the C2H2 zinc fingers of Zif268 to C4 zinc fingers allows proper folding and function of the Zif268 zinc finger domains only if the mutation is present in zinc finger 1 or 3. In contrast, mutation of zinc finger 2 abolishes binding, which is likely a result of the inability of the protein to form the necessary secondary structure (e.g. Green et al, page 89, paragraph bridging columns). Furthermore, if zinc fingers 1 and 3 were simultaneously mutated, the protein was unable to bind DNA (e.g. Green et al, page 89, paragraph bridging columns). Thus, sequences other than the zinc coordinating residues play a role in determining the secondary structure and

target sequence binding of the polypeptide. A review of the specification identified multiple examples of only one general type of non-canonical zinc finger protein meeting the claim limitations: a zinc finger protein in which the zinc coordinating residues are C2HC. There does not appear to be a description of any other zinc fingers that meet the claim limitations with regard to the zinc coordinating residues and secondary structure. Furthermore, the specification does not describe a structure function correlation for residues that support the formation of the claimed secondary structure when a zinc coordinating residue is altered. Accordingly, in the absence of sufficient recitation of distinguishing characteristics (e.g., specific sequences) drawn to other types of non-canonical zinc fingers which retain the canonical structure using zinc coordinating residues that are neither C2H2 nor C2HC (the only structures whose sequences are specifically described), the specification does not provide adequate written description of the claimed genus which encompasses all non-canonical zinc fingers having the canonical general structure.

With regard to the recitation of "non-naturally occurring zinc finger binding protein," the specification does not describe which zinc fingers proteins are definitively non-naturally occurring because all natural proteins are no known. Further, natural proteins encompass proteins that result from mutations that naturally occur such as point mutations and chromosomal translocations. All of the proteins not previously described which are naturally occurring are simply unpredictable because, for example, such proteins encompass proteins from mutant genes. Further, some mutant genes may result from the fusion of DNA binding domains and regulatory domains to two different proteins. Accordingly, in the absence of sufficient recitation of distinguishing characteristics (distinguishing the isolated polynucleotide molecules that

encode non-natural proteins from those that encode natural proteins), the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of non-canonical zinc fingers as claimed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polynucleotides encoding a non-canonical zinc finger, wherein the zinc coordinating residues are drawn to the C2HC structure (and having the other claim limitations) but not the full breadth of the claims meets the written description provision of 35

U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim 53 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new rejection.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claim, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claim, with the most relevant factors discussed below.

Nature of the invention: The claim is drawn to a pharmaceutical composition comprising an isolated polynucleotide encoding a non-naturally-occurring zinc-finger binding protein comprising a non-canonical zinc finger component and a pharmaceutical excipient. The claim encompasses a large genus of polynucleotides encoding zinc finger proteins that contain a non-canonical zinc finger component that contains a bet turn comprising two amino-terminal zinc coordinating cysteine or histidine residues and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine or histidine residues, wherein at least one of the amino-terminal zinc coordinating residues is a histidine residue, or at least one of the carboxy-terminal zinc coordinating residues is a cysteine residue, and the protein is engineered to bind to a target

sequence. Thus, the claim encompasses zinc finger proteins capable of binding to undefined target sequences. The specification envisions using the claimed pharmaceutical composition for gene therapy applications.

The nature of the subject matter is complex, because the nucleic acid must modulate transcription of genes such that a therapeutic outcome is achieved. Furthermore, the nucleic acid molecule must be delivered at a level sufficient to produce a therapeutic outcome (see the discussion below).

Breadth of the claim: The claim is broad in that it encompasses polynucleotides that encode zinc finger proteins that comprise any number of zinc finger components and are capable of binding any target sequence for any gene or chromosomal locus. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

State of the art: An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature, Vol. 389, pages 239-242, 1997; e.g. page 239, paragraph 1) and Palù et al (J. Biotechnol. Vol. 68, pages 1-13, 1999; e.g. Abstract) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicate that most approaches suffer from poor efficiency and transient expression of the gene (e.g. page 239, right column, paragraph 2). Likewise, Luo et al (Nature Biotechnology, Vol. 18, pages 33-37, 2000) indicate that non-viral synthetic delivery systems are very inefficient (e.g. Abstract; page 33, left column, paragraphs 1 and 2). Regarding viral methods for gene

delivery *in vivo*, Verma et al, indicate that lentiviral, adenoviral and AAV vectors are capable of delivery genes, but there is a possibility for insertional mutagenesis or toxicity due to an inflammatory response (e.g. Table 2).

Predictability of the art: The area of the invention is unpredictable. As discussed above, the method of *in vivo* gene therapy is highly complex and unpredictable. Indeed, recent gene therapy protocols have demonstrated unpredictable outcomes resulting from an unexpected inflammatory reaction to an adenoviral vector in a patient and the insertional mutagenesis of a gene resulting in a leukemia-like condition in children being treated for severe combined immunodeficiency (Edelstein et al, J. Gene Med. Vol. 6, pages 597-602, 2004; e.g. page 599, The hopes and the setbacks). The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

Guidance of the specification: The specification envisions the use of the nucleic acid molecules encoding modified zinc finger fusion proteins to modulate the expression of a target gene in the form of repression or activation. The specification envisions the repression of target genes that reside in a pathological infecting microorganism, or an endogenous gene of a patient, such as an oncogene or viral receptor that is contributing to a disease state (e.g. page 42, lines 8-20). Regarding gene activation, the specification envisions the use of the nucleic acid molecules to increase expression of an endogenous cellular gene such as a tumor suppressor gene (e.g. page 42, lines 8-20). The specification envisions using viral and non-viral gene delivery methods for *in vivo* and *ex vivo* gene therapy applications (e.g. pages 34-39). The specification does not disclose which non-canonical zinc finger proteins would be capable of treating specific diseases.

Furthermore, the teachings of the specification do not address the art-recognized obstacles to gene therapy.

Existence of working examples: The specification does not contain any working examples that demonstrate a therapeutic outcome with any polynucleotide encoding any zinc finger for any disease in any model system.

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use the claimed methods. With any disease, infectious or genetic, one would first need to determine which gene(s) may be repressed or expressed to provide a therapeutic outcome. Next, one would need to determine which sequences could be used to modulate transcription of the gene with specificity. Furthermore, with any nucleic acid one would have to determine how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claim 53 is not considered to be enabled by the instant specification.

Response to Arguments - 35 USC § 112

Applicant's arguments filed 3/27/2006 have been fully considered but they are not persuasive.

The response asserts that it is well known in the art (e.g. Rhodes et al, Reference C114 of the IDS filed 5/11/2005) and taught in the specification that cysteine and histidine are the zinc-coordinating residues in zinc fingers, and thus it would be clear to one of skill in the art that the claimed non-canonical zinc fingers are capable of adopting the zinc finger structure. Further, the response asserts that the structure of the zinc finger is well correlated with its ability to bind a target sequence.

This is not found persuasive because sequences other than the zinc coordinating residues are required for the determination of the claimed secondary structure, and the specification does not describe a structure/function correlation such that one could envision all necessary sequence modifications to obtain the claimed secondary structure and function commensurate in scope with the claimed primary zinc finger sequence. While cysteine and histidine are both known to coordinate zinc atoms in the context of properly folded zinc fingers, these critical amino acids are not predictably interchanged (Green et al. Biochem J., Vol. 333, pages 85-90, 1998). For example, Green et al teach that the conversion of the C2H2 zinc fingers of Zif268 to C4 zinc fingers allows proper folding and function of the Zif268 zinc finger domains only if the mutation is present in zinc finger 1 or 3. In contrast, mutation of zinc finger 2 abolishes binding, which is likely a result of the inability of the protein to form the necessary secondary structure (e.g. Green et al, page 89, paragraph bridging columns). Furthermore, if zinc fingers 1 and 3 were simultaneously mutated, the protein was unable to bind DNA (e.g. Green et al, page 89,

paragraph bridging columns). Thus, the primary structure of the C4 zinc finger is not a reliable predictor of secondary structure. The specification provides evidence that C2H2 zinc fingers may be converted to C2HC zinc fingers and maintain the claimed secondary structure, as evidenced by DNA binding in transcription activation assays. However, the data provided by the disclosed C2HC zinc fingers cannot be extended to the other non-canonical zinc fingers encompassed by the claims. Therefore, the specification does not provide adequate written description for all non-canonical zinc finger components encompassed by the rejected claims.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 4, 26-28, 30-32 and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Green et al (Biochem J., Vol. 333, pages 85-90, 1998; see the entire reference). This is a new rejection.

Regarding claim 30, Green et al teach an isolated polynucleotide encoding a modified zif268 zinc finger binding protein, which contains a mutation of the C2H2 motif to a C4 motif in the first or third zinc finger (e.g. page 87, Results). In the C4 motif of Green et al, the zinc coordinating residues are two amino-terminal cysteine residues and two carboxy-terminal

cysteine residues, and thus one of the carboxy-terminal zinc coordinating residues is a cysteine. The modified zif268 zinc finger binding proteins are engineered to bind to the wild type zif268 target DNA sequence 5'-GCGTGGGCG-3' (e.g. paragraph bridging pages 87-88; page 87, right column, 1st full paragraph; Figure 2, especially lanes c and e). Chen et al teach that the mutations allowed for proper folding of the zinc fingers to form a beta turn comprising two amino-terminal zinc coordinating cysteine or histidine residues and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine or histidine residues, which is indirectly evidenced by the ability of the expressed protein to bind DNA (e.g. paragraph bridging pages 88-89). Thus, Chen indirectly provides evidence that the modified zif268 proteins comprise a non-canonical zinc finger component that contains a beta turn and an alpha helix that coordinate zinc using the four cysteine residues.

Regarding claim 31, Green et al teach the Pharmacia pGEX-3X expression vector comprising the isolated polynucleotide (e.g. paragraph bridging pages 86-87; page 87, RESULTS).

Regarding claim 32, Green et al teach *Escherichia coli* bacterial strain BL21(DE3) comprising the expression vector (e.g. page 87, left column, 1st full paragraph).

Regarding claims 2, 4 and 27, the target sequence 5'-GCGTGGGCG-3' taught by Green et al is a DNA sequence consisting of 9 contiguous base pairs (e.g. paragraph bridging pages 87-88; page 87, left column, 2nd full paragraph, and right column, 1st full paragraph).

Regarding claim 26, Green et al teach the isolated polynucleotide, wherein the modified zif268 zinc finger binding protein contains three zinc finger components (e.g. paragraph bridging pages 87-88).

Regarding claim 28, Green et al teach the isolated polynucleotide, wherein the third zinc finger contains the C4 motif (e.g. paragraph bridging pages 87-88).

Regarding claim 54, Green et al teach the isolated polynucleotide, wherein the first zinc finger contains the C4 motif (e.g. paragraph bridging pages 87-88).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25, 36 and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al (Biochem J., Vol. 333, pages 85-90, 1998; see the entire reference) in view of Pomerantz et al (Science, Vol. 267, No. 5194, pages 93-96, 1995; see the entire reference).

The teachings of Green et al are described above and applied as before.

Green et al do not teach the isolated polynucleotide further comprising an activation domain, wherein the target sequence is a promoter sequence.

Pomerantz et al teach the design of a polynucleotide encoding an artificial transcription factor comprising zinc fingers 1 and 2 of Zif268, and the Oct-1 homeodomain (e.g. paragraph bridging pages 93-94). Pomerantz et al teach that the artificial transcription factor expressed from the polynucleotide is capable of binding to a hybrid DNA binding site with the sequence 5'-AAATNNTGGGCG-3' *in vitro* (e.g. page 93, paragraph bridging columns; Figure 3). To determine whether the DNA binding protein could function *in vivo* Pomerantz et al fused the polynucleotide encoding the artificial transcription factor DNA binding domain to a VP16 transcription activation domain to create a polynucleotide encoding ZFHD1-VP16, which was inserted into an expression vector, and cotransfected into 293 cells with a reporter construct (e.g. page 95, paragraph bridging middle and right columns). The reporter constructs taught by Pomerantz et al contain a promoter comprising two copies of the hybrid DNA binding sites (e.g. page 95, paragraph bridging middle and right columns). Further, Pomerantz et al teach that the assays were conducted *in vivo* to determine whether the fusion protein could specifically regulate gene expression and can be used with other engineered proteins (e.g. page 95, right column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide and target sequence of Green et al to include the VP16 activation domain and the location of the target site in the promoter as taught by Pomerantz et al because Green et al and Pomerantz et al teach it is within the ordinary skill in the art to engineer an artificial transcription factor and study the binding of the transcription factor to its cognate DNA binding site.

One would have been motivated to make such a modification in order to receive the expected benefit of determining whether the modified zif268 transcription factor taught by Green et al is capable of specifically binding its target sequence *in vivo*. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 22 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al (Biochem J., Vol. 333, pages 85-90, 1998; see the entire reference) in view of Pomerantz et al (Science, Vol. 267, No. 5194, pages 93-96, 1995; see the entire reference) as applied to claims 25, 36 and 39-41 above, and further in view of Guyer et al (Genetics, Vol. 149, pages 633-639, 1998; see the entire reference).

The combined teachings of Green et al and Pomerantz et al are described above and applied as before.

Green et al and Pomerantz et al do not teach the polynucleotide comprising a maize C1 activation domain and do not teach a plant cell comprising the target sequence.

Guyer et al teach *Arabidopsis* plants comprising a stably integrated hybrid transcription factor, and plants comprising an activatable transgene, where the hybrid transcription factor and activatable transgene are brought together in the same cell by fertilization (e.g. paragraph bridging pages 633-634). Specifically, Guyer et al teach a GAL4 DNA binding domain fused to a maize C1 transcription activation domain as the hybrid transcription factor, and a reporter transgene controlled by a synthetic promoter comprising ten GAL4 DNA binding sites (e.g.

paragraph bridging pages 633-634; Figure 1). Further, Guyer et al teach that many positive transcriptional regulatory factors are modular, consisting of a DNA-binding domain and an activation domain and that fusing combinations of these elements derived from different kingdoms results in the production of diverse hybrid factors having defined DNA-binding specificity and transcriptional activation function with advantages over expression under direct control by a natural promoter (e.g. page 633, left column; page 638, paragraph bridging columns).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide and target sequence of Green et al to include the VP16 activation domain and the location of the target site in the promoter as taught by Pomerantz et al because Green et al and Pomerantz et al teach it is within the ordinary skill in the art to engineer an artificial transcription factor and study the binding of the transcription factor to its cognate DNA binding site. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide to comprise a C1 activation domain taught by Guyer et al and to use a plant cell comprising the modified zif268 cognate DNA binding site because Green et al and Pomerantz et al teach it is within the ordinary skill in the art to engineer an artificial transcription factor and study the binding of the transcription factor to its cognate DNA binding site and Pomerantz et al and Guyer et al teach it is within the ordinary skill of the art to test transcription factor DNA binding *in vivo* in a cultured cell.

One would have been motivated to make such a modification in order to receive the expected benefit of determining whether the modified zif268 transcription factor taught by Green et al is capable of specifically binding its target sequence *in vivo* in a plant cell thus expanding

the number of species in which the modified zif268 transcription factor can be used. Further, one would be modified to use the modified mammalian zif268 DNA binding domain in a plant cell because Guyer et al teach that proteins from different kingdoms may be combined to create hybrid transcription factors for use in plants, and that these hybrid transcription factors may provide specific gene activation in plants. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 25, 36, 39-41 and 55 is rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al (Biochem J., Vol. 333, pages 85-90, 1998; see the entire reference) in view of Barbas, III et al (US Patent No. 6,242,568, cited as reference A39 on the IDS filed 5/11/2005; see the entire reference). This is a new rejection.

The teachings of Green et al are described above and applied as before.

Green et al do not teach the polynucleotide further comprising a fourth zinc finger, wherein the zinc fingers are fused to an activation domain. Green et al do not teach the location of target site located within a promoter.

Barbas, III et al teach polynucleotides encoding zinc finger binding polypeptide variants, including expanded polypeptides (e.g. column 8, lines 55-60). The variant polypeptides encoded by the polynucleotides of Barbas, III et al bind to either DNA or RNA and may enhance or suppress transcription from a promoter. Barbas, III et al teach that "expanded" proteins are zinc finger polypeptides to which additional zinc finger modules have been added (e.g. column 7, lines 25-40). Examples of proteins that may be expanded include TFIIIA and zif268 (e.g.

column 7, lines 49-55). Further, Barbas, III et al teach that the expanded zinc finger proteins may also be mutagenized (e.g. column 7, lines 20-55). Barbas, III et al teach that expanded zinc finger domain polypeptides comprising 2 to 12 zinc fingers derived from Zif268 can be fused to the leucine zipper domains of the Jun/Fos proteins, and may further include activation domains to produce activators of transcription (e.g. Example 12). Further, Barbas, III et al teach that these heterodimeric Zif constructs are advantageous since they allow for extended palindromic sequences (e.g. Example 12).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide encoding the zinc finger polypeptide of Green et al to include up to 12 zinc fingers, a leucine zipper and an activation domain as taught by Barbas, III et al because Green et al and Barbas, III et al teach it is within the ordinary skill in the art to engineer Zif268 zinc finger proteins. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide the target site for the protein of Green and Barbas, III et al in a promoter because Barbas, III et al teach it is within the skill of the art to activate transcription from a promoter.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to activate gene transcription from an extended palindromic sequence in a promoter as taught by Barbas, III et al. This would allow one to activate transcription more specifically from a sequence that occurs less frequently in a genome of a cell than the shorter binding site taught by Green et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the

contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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